BRAG2 INHIBITORS AND APPLICATIONS THEREOF

[0001] The present invention concerns molecules, in particular active as BRAG2 inhibitors and applications thereof.

[0002] In particular, the invention concerns BRAG2 inhibitors in the treatment of a cancer or angiogenesis.

PRIOR ART

[0003] Cells response to variations in their environment by assembling dynamic signalling complexes at the surface of membranes, which collect signals and transmit information. Such signalling platforms are often dysfunctional in disease, either because of mutations that affect their regulation or because they are appropriated by pathological pathways. Drugs modulating their activity are thus highly sought-after, but signalling nodes have remained challenging targets by conventional competitive inhibitors because of their structural flexibility, which commonly involves large conformational changes, their widespread protein-protein interfaces and their multiple protein-lipid interactions. Consequently, a current drug discovery challenge is to develop novel strategies that use the structural features of membrane-associated signalling complexes.

[0004] Small GTPases and their regulators belong to the category of peripheral membrane proteins involved in pathologies. Proteins of the large family of small GTPases are chief organizers of signalling platforms at the surface of membranes with crucial functions in signal transduction, cell motility, membrane traffic and the coordination between these pathways. Because of their importance in normal cell homeostasis, small GTPase functions are twisted or hijacked in diverse pathologies, such as cancer, cardiovascular diseases and bacterial or viral infections. Inhibiting their activities in pathological contexts is therefore a compelling, unmet need in drug discovery. Small GTPases regulation is highly complex as it combined a GDP/GTP switch and a cytosol/membrane cycle where the GTP-bound GTPase is attached to the membrane. Added to this, the output of GTPase signalling involves multiple activators (guanine nucleotide exchange factors or GEFs, which stimulate the GDP/GTP exchange), inhibitors (GTPase-activating proteins or GAPs, which accelerate GTP hydrolysis and GDIs, which wrap their lipidic anchor to solubilize them), and effectors, which collectively assemble signalling platforms. GEFs, GAPs and effectors are themselves highly regulated through structural rearrangements and protein-membrane interactions. To date, some strategies inhibit the membrane/cytosol cycle by targeting either enzymes involved in the anchoring of their lipid post-translational modification or GDIs. Yet, inhibitors that directly target the regulatory protein-membrane interactions have never been described.

[0005] Peripheral membrane proteins coordinate cell responses to signals coming from their environment and are hence involved in numerous diseases. Despite their significance, they have remained elusive targets for conventional competitive inhibitors and alternate approaches are highly needed.

Aims of the Invention

[0006] The present invention aims to solve the technical problem of providing a BRAG2 inhibitor and applications thereof.

[0007] The present invention aims to solve the technical problem of providing new route for the treatment of a cancer or angiogenesis.

[0008] More particularly, the present invention aims to solve the technical problem of providing new route for the treatment of a cancer or angiogenesis by a BRAG2 inhibitor.

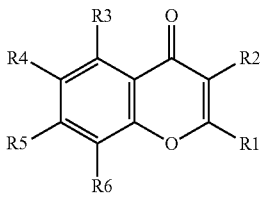
[0009] The present invention also aims to solve the technical problem of providing a molecule binding a protein-membrane interface.

DETAILED DESCRIPTION

[0010] The present invention solves at least one and preferably all technical problem set forth in the present invention.

[0011] In particular, the present invention relates to molecules having the following chemical structure (I) or a pharmaceutically acceptable salt thereof or a prodrug thereof, for use in a method of therapeutic treatment:

(I)



wherein:

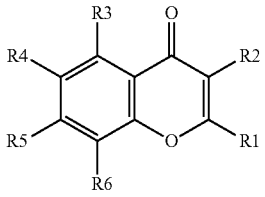
R1 is a fluorinated alkyl, preferably CF3;

R3 is a chemical group comprising at least one oxygen and/or a nitrogen;

R2, R4, R5 and R6 are independently atoms or groups of atoms.

[0012] The invention also relates to molecules having the following chemical structure (I):

(I)



wherein:

R1 is a fluorinated alkyl, preferably CF3;

R3 is a chemical group comprising at least one oxygen and/or a nitrogen;

R6 is an atoms or group of atoms different than hydrogen;

R2, R4, R5 and are independently atoms or groups of atoms.

[0013] In particular, the present invention relates to a BRAG2 inhibitor having a structure of a molecule as defined in the present invention.

[0014] BRAG2 designates the protein Brefeldin-resistant Arf-GEF 2 protein (SEQ ID NO:1) (IQ motif and SEC7 domain-containing protein 1, i.e. see UniProtKB—Q6 DN90 (IQEC1_HUMAN)—SEQ ID NO:1). This protein is also designated as ADP-ribosylation factors guanine nucleotide-exchange protein 100 or ADP-ribosylation factors gua-